REMARKS

I. Claims in the Case

Claims 9 and 22 have been amended and claims 52–55 have been added. Claims 2-41 and 52-55 are currently pending.

Support for the amendment to claim 9 can be found in the specification, for example, at page 5, line 20. Support for new claims 52-55 can be found in the specification at, for example, in the sentence bridging pages 5 and 6, as well as Example 7.

II. Rejection of Claims Under 35 U.S.C. § 112, 2nd Paragraph.

The Action has rejected claims 9 and 22 under 35 U.S.C. § 112, 102nd paragraph. Applicants have proceeded to amend each of the claims in the manner believed to be consistent with the Examiner's suggestions. Applicants appreciate the Examiner's recommendations and find them to be appropriate. It is believed that each of these amendments address matters of a formalistic nature and not substantive and do not impinge upon the scope of the claims.

III. Rejection of Claims 2-5, 10-12 and 33-41 under 35 U.S.C. § 103(a) Over Ilgan, *et al.*

The Action next rejects claims 2-5, 10-12 and 33-41 as obvious over the Ilgan, *et al.* reference, published December 1998.

In response, Applicants submit that the Ilgan, *et al.* reference would only be an obviating reference with respect to the specific subject matter that it discloses, Tc-99m etchylenedicysteine(EC)-folate as a tumor imaging agent. It is respectfully submitted that Ilgan, *et al.* can in no way be considered obviating for distinct species of targeted ECs, as the Action has failed to cite to any art, other than that discussed below, that would teach or suggest other EC targeting agents, or that teach or suggest other targeting agents that could appropriately or

effectively be used to target EC. Moreover, there has been no art cited for motivation to combine a targeting agent other than folate to Tc-99m EC for targeting purposes.

Nevertheless, it is respectfully submitted that Ilgan, *et al.* is not available as prior art on the basis that none of the non-inventor authors of the Ilgan, *et al.* reference can be considered inventors of the subject matter of dependent claims. This is demonstrated by virtue of the enclosed declaration of the inventors, which demonstrates the role that each of the non-inventor authors played with respect to the subject matter of Ilgan, *et al.*, and demonstrate that the contribution of these individuals can in no way be considered inventive and, further, that these individuals worked under the direction or control of one or more of the named inventors. As such, the Ilgan, *et al.* reference is not available as prior art against claims supported by the original parent specification. It is believed that all of the pending claims are supported by the parent '313 specification, with the possible exception of claims directed to ligands that mimic glucose, such as covered by claims 5, 24, and new claims 52-55. Nevertheless, the subject matter of these claims are clearly patentable over the Ilgan article.

IV. Rejection of Claims 33-38 under 35 U.S.C. § 103(a) over Mangera, *et al.*

The Action has rejected Claims 33-38 as obvious over the Mangera, *et al.* article, which is said to disclose the synthesis and evaluation of Tc-99m ethylene dicysteime (EC) as a possible label for bio-active compounds, such as peptides, diphosphonates and other compounds. The Action concedes that the reference fails to disclose a specific example wherein a bio-active compound is attached to the 99mTc-EC.

It is first respectfully submitted that the Mangera, *et al.* article only makes a passing reference to the possibility of linking 99mTc to an EC compound for the purpose of bio-active compounds. The article merely states that such a possibility "looks promising." As such, it is

respectfully submitted that it is insufficient to form the basis of a *prima facie* case of obviousness. The Action cites to no secondary references for this possibility, and there is no teaching, other than in the references addressed herein, as to how one would go about carrying such a suggestion out. As such, the Mangera, *et al.* article can only be considered a "obvious to try" reference. As framed by the Action, the rejection is improper as a matter of law. Applicants turn to *In re O'Farrell*, 7 USPQ2d 1673 (Fed. Cir. 1988), which held that, in order for a reference or references to obviate an invention, it must be shown that the reference (or references) contains:

(1) detailed enabling methodology for practicing the claimed invention;

(2) a suggestion for modifying the prior art to practice the claimed invention; and

(3) evidence suggesting that the invention would be successful.

It is submitted that the present references relied upon by the Examiner clearly fail to satisfy this tripartite test of *O'Farrell*. In particular, for the reasons discussed above, none of the references provides a reasonable expectation that such a combination would be successful and they fail to provide detailed enabling methodology practicing the claimed invention, e.g., for constructing the claimed conjugate. Moreover, there is no evidence that such a conjugate, once constructed, would actually function appropriately and that it would remain stable in the body as required.

In the more recent case of *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991), the Federal Circuit took the *O'Farrell* doctrine a step further. In *Vaeck* the Federal Circuit stated that in order for an examiner to make out a *prima facie* case of obviousness two things must be shown:

(1) that the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition; and

(2) that the prior art must demonstrate a reasonable expectation of success of the invention.

The court went on to emphasize that both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. Here, for the reasons discussed above, we have neither.

Furthermore, Applicants respectfully submit that the Mangera, *et al.* article is not available as prior art. In the enclosed declaration, it is demonstrated that, by reference to the present inventors earlier publication (Ilgan, *et al.*, *Cancer Biother. Radiopharm.*, December, 1998), that the present inventors had actually reduced a species within the subject matter of the broadest claim, demonstrating that the present invention had been made in this country prior in time to the publication date of the Mangera, *et al.* article. Accordingly, Mangera, et al. is not available under 35 U.S.C. § 1.02(a), or any other section or subsection of section 102, against claims supported by the original parent specification. It is believed that all of the pending claims are supported by the parent '313 specification, with the possible exception of claims directed ligands that mimic glucose, such as covered by claims 5, 24, and new claims 52-55. Nevertheless, the subject matter of these claims are clearly patentable over the Mangera *et al.* article.

V. Rejection of Claims 2-5, 15, 16, 18 and 33-38 under 35 U.S.C. § 103(a) over Zareneyrizi, *et al.*

The Action next rejects Claims 2-5, 15, 16, 18 and 33-38 as obvious over the Zareneyrizi, *et al.* reference.

In response, Applicants submit that the Zareneyrizi, *et al.* reference would only be an obviating reference with respect to the specific subject matter that it discloses, Tc-99m ethylene dicysteine(EC)-colchicine for evaluation of its antiangiogenic activity. It is respectfully

submitted that Zareneyrizi, *et al.* can in no way be considered obviating for distinct species of targeted ECs, as the Action has failed to cite to any art, other than that discussed herein, that would teach or suggest other EC targeting agents, or that teach or suggest other targeting agents that could appropriately or effectively be used to target EC. Moreover, there has been no art cited in this particular rejection for motivation to combine a targeting agent other than colchicine to Tc-99m EC for targeting purposes.

Nevertheless, it is respectfully submitted that Zareneyrizi, *et al.* is not available as prior art on the basis that none of the non-inventor authors of the Zareneyrizi, *et al.* reference can be considered inventors of the subject matter of dependent claims. This is demonstrated by virtue of the enclosed declaration of the inventors, which demonstrates the role that each of the non-inventor authors played with respect to the subject matter of Zareneyrizi, *et al.*, and demonstrate that the contribution of these individuals can in no way be considered inventive and, further, that these individuals worked under the direction or control of one or more of the named inventors. As such, the Zareneyrizi *et al.* reference is not available as prior art against claims supported by the original parent '313 specification. It is believed that all of the pending claims are supported by the parent '313 specification, with the possible exception of claims directed to ligands that mimic glucose, such as covered by claims 5, 24, and new claims 52-55. Nevertheless, the subject matter of these claims are clearly patentable over the Zareneyrizi *et al.* article.

VI. Rejection of Claims 2-5, 15, 16 and 33-38 under 35 U.S.C. § 103(a) over Yang, *et al.*

The Action next rejects Claims 2-5, 15, 16 and 33-38 as obvious over the Yang, *et al.* reference.

In response, Applicants submit that the Yang, *et al.* reference would only be an obviating reference with respect to the specific subject matter that it discloses, Tc-99m ethylene

dicysteine(EC)-metranidazole as an imaging agent to image tumor hypoxia. It is respectfully submitted that Yang, *et al.* can in no way be considered in and of itself as obviating for distinct species of targeted ECs, as the Action has failed to cite to any art, other than that discussed herein, that would teach or suggest other EC targeting agents, or that teach or suggest other targeting agents that could appropriately or effectively be used to target EC. Moreover, there has been no art cited in this particular rejection for motivation to combine a targeting agent other than metranidazole to Tc-99m EC for targeting purposes.

Nevertheless, it is respectfully submitted that Yang, *et al.* is not available as prior art on the basis that none of the non-inventor authors of the Yang, *et al.* reference can be considered inventors of the subject matter of dependent claims. This is demonstrated by virtue of the enclosed declaration of the inventors, which demonstrates the role that each of the non-inventor authors played with respect to the subject matter of Yang, *et al.*, and demonstrate that the contribution of these individuals can in no way be considered inventive and, further, that these individuals worked under the direction or control of one or more of the named inventors. As such, the Yang, *et al.* reference is not available as prior art against claims supported by the original parent specification. It is believed that all of the pending claims are supported by the parent '313 specification, with the possible exception of claims directed to ligands that mimic glucose, such as covered by claims 5, 24, and new claims 52-55. Nevertheless, the subject matter of these claims are clearly patentable over the Yang *et al.* article.

VII. Rejection of Claims 2, 3, 33 and 34 under 35 U.S.C. § 103(a) over Anderson, *et al.*

The Action next rejects claims 2, 3, 33 and 34 as obvious over the Anderson, *et al.* reference, taking the position that Anderson discloses labeled EC complexes for *in vivo* studies. The Action concludes that the addition of a tissue-specific ligand would be obvious since "the

prior art suggests that EC derivatives are stable *in vivo*, derivatives of EC may have application as bi-functional keylates for proteins and peptides."

Applicants respectfully traverse. It is first respectfully submitted that the Anderson, *et al.* article only makes reference to the observation that a indium complex with excellent in vivo stability "is desirable when designing bifunctional chelates to be conjugated to larger molecules such as antibodies or peptides." (page 165, col. 1) However, this statement does not identify EC conjugates *per se*, and, more importantly, the article itself suggests that it would be unpredictable whether a chelate conjugated to a protein or peptide would be stable *in vivo* ("the nature of the bifunctional chelate use to complex radiometals to proteins or peptides also alters the uptake and in clearance organs..." page 165, sentence bridging columns 1 and 2).

In the Conclusion section, the article states that "[i]t would be interesting to compare the biodistribution" of an indium labeled EC analogue conjugated to a "protein or peptide" or other indium labeled conjugates. (page 172, col. 2) However, the article further teaches the uncertainty of whether such conjugates would prove to have sufficient stability, noting that "[t]he accumulation of radiolabeled ligand complexes in the liver without clearance may be indicative of complex instability" and that "[t]his needs to be further investigated" (page 172, col. 1).

From the foregoing passages, it appears that the authors simply do not have any degree of certainty whether EC conjugates would be sufficiently stable to be useful. They merely state, in effect, that it would be "interesting" to find out the answer to this question. Accordingly, Anderson *et al.*, similar to Mang'era, *et al*, as discussed above, is nothing more than an "obvious to try" reference. As framed by the Action, the rejection is improper as a matter of law. Applicants turn to *In re O'Farrell*, 7 USPQ2d 1673 (Fed. Cir. 1988), which held that, in order

for a reference or references to obviate an invention, it must be shown that the reference (or references) contains:

(1) detailed enabling methodology for practicing the claimed invention;

(2) a suggestion for modifying the prior art to practice the claimed invention; and

(3) evidence suggesting that the invention would be successful.

It is submitted that the present references relied upon by the Examiner clearly fail to satisfy this tripartite test of *O'Farrell*. In particular, for the reasons discussed above, none of the references provides a reasonable expectation that such a combination would be successful and they fail to provide detailed enabling methodology practicing the claimed invention, e.g., for constructing the claimed conjugate. Moreover, there is no evidence that such a conjugate, once constructed, would actually function appropriately and that it would remain stable in the body as required.

In the more recent case of *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991), the Federal Circuit took the *O'Farrell* doctrine a step further. In *Vaeck* the Federal Circuit stated that in order for an examiner to make out a *prima facie* case of obviousness two things must be shown:

(1) that the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition; and

(2) that the prior art must demonstrate a reasonable expectation of success of the invention.

The court went on to emphasize that both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. Here, for the reasons discussed above, we have neither.

VIII. Rejection of Claims 2-5 and 33-38 under 35 U.S.C. § 103(a) over Anderson, *et al.*, in view of Marzilli, *et al.* or Bergstein, *et al.*

The last rejection raised by the Action is similar to the foregoing rejection based on Anderson, *et al.*, but incorporates two secondary references, Marzilli, *et al.* or Bergstein, *et al.* For the reasons discussed below, it is respectfully submitted that these references fail to provide any further teaching or suggestion that would, in light of Anderson, *et al.*, render the claimed invention obvious.

Applicants would first incorporate by reference the above response with respect to the Anderson, *et al.*, reference.

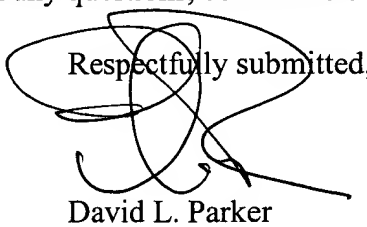
With respect to the secondary references, the Action first refers to the Bergstein *et al.* reference which is said to disclose diaminodithiols and radiolabeled complexes thereof. Bergstein et al. is apparently cited for the fact that the idea of making radioimaging kits is known in the art. Applicants respond by noting that while such a concept may *generally* be known, it is not known in the context of EC conjugates with targeting ligands, and Bergstein *et al.* fails to provide any such teaching or suggestion.

Next, that Action refers to the Marzilli *et al.*, reference, which is said to disclose imaging agents comprising EC and derivatives chelated with radiolabeled 99m-Tc. Similar to Bergstein, *et al.*, Marzilli *et al.* is apparently being cited for the concept that kits were known in the context of radioimaging. As noted above, while such a concept may *generally* be known, it is not known in the context of EC conjugates with targeting ligands, and Marzilli *et al.* fails to provide any such teaching or suggestion. Notably, as the Action appears to concede, Marzilli, *et al.* fails to teach or suggest conjugating the radiolabeled EC to a targeting ligand. For this reason, Marzilli et al. is no more relevant that Anderson, *et al.*

IX. Conclusion

For the foregoing reasons, the Examiner respectfully is requested to reconsider the rejections and find that the application is condition for allowance. The Examiner should feel free to contact the undersigned representative if any questions, comments or suggestions arise.

Respectfully submitted,



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CLAIM AMENDMENTS

9. The method of claim 8, wherein said tumor marker is PSA, ER, PR, CA-125, CA-199, CEA AFP, interferons, BRCA1, HER-2/neu, cytoxan, p53, endostatin, ~~or~~ a monoclonal antibody or ~~(e.g.~~ an antisense~~)~~.

22. The method of claim ~~0~~ 21, wherein the ligand derivative is 99mTc-EC-glutamate pentapeptide.